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## Description

This invention relates to an injectable composition comprising polymeric bodies, particularly deformable hydrogel macrodisks. The invention is also concerned with a process for preparing said composition.

The use of various injectable or inflatable polymeric bodies for tissue augmentation and prosthetic implants is known in the art. For example EP-A-0251695 discloses injectable implant compositions for soft tissue augmentation, comprising an aqueous suspension of a particulate biocompatible material and a sufficient amount of a biocompatible fluid lubricant to improve the intrudability of said compositions into the soft tissue, whilst US Patent No 4,686,962 discloses an assembly for hypodermically implanting a genitourinary prosthesis for the treatment of urinary incontinence which includes an inflatable containment membrane which is inflated by material injected with a hypodermic needle.

Urinary incontinence also has been treated by the transurethral injection of polytetrafluoroethylene (PTFE), usually in the form of a paste or encapsulated particles. See, for example, "Transurethral Polytetrafluoroethylene Injection for Post-prostatectomy Urinary Incontinence" by M. Kaufman et al, the *Journal of Urology*, Vol. 132, September 1984, p. 463-464, and the references cited therein. However, if the particles are small, complications arise from undesirable migration or removal by phagocytes causing potential problematical accumulation at other sites, for example the brain, kidney or lungs.

Another application for tissue augmentation is in the treatment of a hypoplastic breast wherein a typical prior art prosthesis is provided by a silicone membrane enveloping a suitable bulking material, for example a saline solution or a flexible polysiloxane gel. One disadvantage of the saline-containing prosthesis is that microleaks in the silicone membrane or valving mechanism lead to deflation of the prosthesis. A problem with polysiloxane gel is that it contains low-molecular weight compounds, such as cyclic oligomers, which slowly migrate into the patient's system and cause problems similar to those associated with the PTFE particles discussed above.

A solution to the problems associated with earlier polymeric implants is provided by US Patent No. 4,631,188, which discloses a method of *in situ* formation of a solid polymer in a mammal which comprises injecting into said mammal a physiologically-acceptable polymeric composition comprising a solution in a water-soluble, non-toxic polar solvent of a water-insoluble, non-toxic, non-cross-linked polymer or copolymer selected from polymers and copolymers of acrylonitrile or vinylacetate, linear or slightly branched polymers and copolymers of 2-hydroxyethylacetate and methacrylate, poly-(N-vinyliminocarbonyl), polycondensates and polyadducts and having a solubility parameter of from about 9.2 to about 15.5 (cal/cc)<sup>1/2</sup>.

The water-insoluble non-toxic polymers used in the method disclosed in US Patent No. 4,631,188 fall within the class of compounds known in the art as water-swelling hydrogels and the disclosure in said patent relating to this class of compounds is incorporated herein by reference. As noted in the patent, water-swelling hydrogels have been used in the art for tissue augmentation, usually in implants of defined shape and size. The method disclosed in the patent overcomes problems associated with such preformed implants by injecting a solution of said hydrogel into a mammal resulting in the *in situ* formation of a solid polymer in the mammal. This method involves the use of a water-soluble polar solvent, for example dimethyl sulfoxide (DMSO), which, although non-toxic, is an unnecessary adjunct to the implant and has to be dispersed by the mammal's metabolism. Furthermore, since the polymer is water-insoluble but water-swelling, formation of the solid polymer is dependent upon the amount of water present in the mammalian tissue and the size and shape of the implant is difficult to control.

Surprisingly, it has now been found that an injectable composition based upon a water-insoluble, non-toxic hydrogel but not containing undesirable solvents may be provided if the hydrogel is in the form of discrete, deformable bodies as hereinafter described. Moreover, the discrete, deformable bodies, since they already contain their full complement of water, retain their individual identity and are stable after injection so that the size and shape of the implant does not alter.

In accordance with the present invention there is provided an injectable composition consisting of a plurality of discrete physiologically-compatible, non-biodegradable, polymeric bodies, said bodies having (i) an average outside diameter of from about 0.027 to 5.08 mm. (0.005 to 0.20 inch), (ii) reversible deformability of about 20 to 75% of their unstressed outside diameter, and (iii) a lubricious surface.

The invention also provides a process for the preparation of an injectable composition as described above which comprises dissolving a physiologically-compatible, non-biodegradable, water-insoluble, non-cross-linked polymer in a dipolar, aprotic organic solvent, rapidly injecting the resulting solution in a fine stream into a relatively large volume of a liquid medium which is a non-solvent for the polymer while slowly stirring said medium so that discrete bodies of the polymer are formed, washing said bodies until said solvent is removed and recovering bodies of the desired size by filtration through an appropriate sieve.

The injectable composition of the invention consists of discrete bodies of a particular size and possessing

unique characteristics which enable them to be injectable, i.e. to be introduced into and contained within a hypodermic needle, without the aid of a carrier or solvent. Thus the injectable composition may be not in the form of a traditional solution, suspension or paste, but merely may consist of a plurality of the above-described discrete bodies themselves. It is to be noted that a certain amount of liquid, preferably water, must be present to provide the required lubricious surface hereinafter described but, in the case of a water-swallowable hydrogel which has its full complement of water, the required amount of water is already present in the bodies and, accordingly, the addition of a carrier liquid (water) is usually not necessary when the injectable composition is used. Also the polymeric bodies are normally stored in a suitable sterile non-solvent, for example, saline solution, as hereinafter described, so that the saturation amount of water is maintained and there is a negligible possibility of the bodies drying out and losing their lubricious surface. The injectability of the bodies is particularly surprising because in many instances the average size of the bodies is greater than the inside diameter of the needle in which they are to be used. Thus, as more particularly described hereinafter, when the bodies are in the preferred form of macrodisks, the average outside diameter of the macrodisks may be up to about three times the inside diameter of a hypodermic needle through which they may be successfully passed without undergoing observable damage.

The unique and surprising injectability of the discrete bodies which form the composition of the invention may be attributed primarily to the characteristics which are defined herein as reversible deformability and lubricious surface.

As used herein the term "reversible deformability" means that the bodies are sufficiently flexible to be deformed into virtually any shape by folding, compression or both when subjected to the physical stress required to produce the relevant deformation, for example the deformation required to introduce the bodies into a hypodermic needle, but return to their original shape and size when said stress is removed, e.g. when they are expressed from the needle.

It is also essential that each discrete body has a lubricious surface, i.e. said surface must be sufficiently smooth and slippery so that the bodies do not stick to any surface with which they come into contact during the performance of the invention, for example, the inside surface of a hypodermic needle, nor do they stick to themselves. The fact that the bodies do not stick to themselves means that they slip with respect to each other and, when injected, can be contoured or manipulated into any desired shape and subsequently retain their discrete identity and do not form undesirable lumps or agglomerates.

Preferably, the discrete polymeric bodies are made from a water-swallowable hydrogel and a particularly preferred hydrogel is a partially hydrolyzed polyacrylonitrile. This material, when used to prepare bodies by the process according to the invention, provides bodies having the required reversible deformability and lubricious surface described above.

The lubricity of the bodies may be even further enhanced if the bodies include a water-soluble polysaccharide, such as dextran.

The discrete polymeric bodies present in the composition of the invention have an average outside diameter of from about 0.27 to 5.08 mm. (0.005 to 0.20 inch). Thus they are large enough to avoid undesirable migration from the site of injection, which was serious problem with the microparticles, for example PTFE, used in the prior art. However, because of the deformability characteristic described hereinabove, they are still small enough to be injectable without undergoing irreversible damage.

In a particularly preferred embodiment of the invention the bodies are deformable macrodisks having an average outside diameter of from about 0.254 to 2.159 mm. (0.01 to 0.085 inch). Macrodisks having an average diameter at the upper end of the stated range, with a few even as large as 2.54 mm. (0.10 inch) in diameter, may be injected through an 18ga needle (internal diameter 0.884 mm. (0.034 inch)) with no apparent macrodisk damage.

In an alternative embodiment, the bodies may be spherical bodies having an average outside diameter of from about 0.254 - 2.159 mm (0.01 to 0.085 inch). However, with this embodiment, the bodies are less deformable than the macrodisks and the diameter of the needle has to be relatively larger for a similar diameter body.

The unique discrete, deformable and slippery bodies which provide the injectable composition of the invention are prepared by a process which comprises dissolving a physiologically-compatible, non-biodegradable, water-insoluble, non-crosslinked polymer, preferably a water-swallowable hydrogel, in a dipolar aprotic organic solvent, for example dimethyl sulfoxide (DMSO), dimethylformamide or N,N-dimethylacetamide, rapidly injecting the resulting solution in a fine stream, for example through a hypodermic needle, into a relatively large volume of a liquid medium which is a non-solvent for the polymer while slowly stirring said medium so that discrete bodies of the polymer are formed. When the fine stream of solution hits the non-solvent liquid medium the polymer, e.g. hydrogel, forms small bodies and the stirring of the liquid medium prevents these bodies from agglomerating together. Under these conditions it appears that a membrane or hydrogel/liquid interface

forms on the surface of each individual body, the solvent, e.g. DMSO, is expressed from the body leaving a discrete solid body which does not stick to or agglomerate with any adjacent body. The bodies thus formed are then washed, preferably with water or, alternatively with the same non-solvent used in their preparation, to remove all the solvent; and the washed discrete bodies are then recovered by filtration through an appropriate sieve.

In the above described process the non-solvent liquid medium is preferably water, usually distilled water. Other suitable liquids are acetone, low molecular weight alcohols, for example, methanol, ethanol or isopropanol, or mixtures of these liquids with water. Generally, when the non-solvent is water the hydrogel bodies assume the form of flat disks with rounded edges, referred to herein as macrodisks, and these macrodisks generally have an average outside diameter of from about 0.254 to 2.159 mm. (0.01 to 0.85 inch). When the non-solvent is acetone there is a tendency for the bodies to form spheres.

When the bodies are washed and recovered they may be stored in a suitable sterile non-solvent liquid, for example, saline solution.

The injectable composition of the invention is particularly suitable for the treatment of a number of tissue conditions in mammals, particularly humans. The expression "tissue conditions" as used herein is intended to be generic to any situation or condition which requires augmentation, enhancement, medication, strengthening or replacement of tissue, and includes, but is not limited to: tissue augmentation of a hypoplastic breast; transurethral and periurethral injection to treat urinary incontinence; tissue augmentation of scar tissue; and treatment of tissue deficiency arising from severe wounds, e.g. "plastic surgery".

The discrete bodies in the composition are preferably deformable macrodisks of a water-swellaable hydrogel, preferably a partially hydrolyzed polyacrylonitrile having an average molecular weight of from about 100,000 to 150,000, said macrodisks having an average outside diameter of from about 0.254 to 2.159 mm. (0.01 to 0.085 inch). The size of the macrodisks prevents undesirable migration to other parts of the patient's body and the lubricity of the macrodisks allows for manipulation of the injected composition into the desired shape for the prosthesis and affords a tissue-like softness upon manual compression. Since the hydrogel is non-biodegradable, the prosthesis retains its integrity indefinitely.

The invention will be more particularly described with reference to the following Examples which illustrate various embodiments of the invention.

#### Example 1

This Example illustrates a typical procedure for preparing injectable discrete macrodisks from partially hydrolyzed polyacrylonitrile (PHPA).

20g. of ground PHPA was added to a beaker containing 180g. of DMSO and the mixture stirred at a temperature of 70°C. until the polymer was dissolved. The warm solution was vacuum filtered (5 $\mu$ ) and then rapidly injected through a 25ga needle into a container containing 2.0 liters of distilled water. The water was slowly stirred to ensure singulation of the macrodisks. After the macrodisks were formed they were repeatedly washed with distilled water until substantially all the DMSO was removed. The resulting macrodisks were collected by filtration from water and sieved through a 10 mesh polypropylene screen and collected on an 18 mesh screen. The resulting macrodisks had an average outside diameter of 2.08 mm (0.082 inch), although disks as small as 1.27mm (0.050 inch) and as large as 2.54 mm (0.10 inch) were also present in small quantities. The overall yield was approximately 70% by weight.

#### Example 2

Macrodisks as prepared in Example 1 were steam sterilized in a sealed 20ml. glass vial containing 30% w/w distilled water. The sterilized macrodisks were placed into a 3ml. plastic syringe and, using only moderate finger pressure, were injected through an 18ga needle with no apparent macrodisk damage.

#### Example 3

Macrodisks as prepared in Example 1 were mixed with 30% w/w of a 25% (w/w) dextran (Sigma, clinical grade, MW 77,800) aqueous solution. After steam sterilization in a sealed 20ml. glass vial, the macrodisks were placed in a 3ml. plastic syringe and the material was expressed with only moderate finger pressure through an 18ga needle. The presence of dextran, due to its lubrication effect, facilitated injection compared to Example 2.

**Example 4**

Macrodisks as prepared in Example 1 were placed in a 3ml. plastic syringe and steam sterilized in the presence of 30% w/w distilled water as carrier. Varying amounts of the composition (0.20-1.0ml.) were injected subcutaneously in New Zealand white rabbits through an 18ga needle. Injection site biopsies were taken at one week, one month, and three months. Tissue reactions were very mild with a thin, well-defined continuous collagenous capsule observed around the implant material after one month. No evidence of macrodisk migration away from the injection site was observed histologically.

**Example 5**

A solution containing 10% w/w of PHPA in DMSO was rapidly injected through a 25ga needle into 250ml. of slowly stirred acetone. The resulting spherical bodies were separated and screened as in Example 1. The spheres were equilibrated in distilled water, suspended in dextran as described in Example 3, and sterilized in a capped glass vial. The spheres were placed into 1ml. and 3ml. plastic syringes and passed through a 15ga needle using moderate finger pressure.

**Example 6**

A comparison of PHPA macrodisks and spheres was made to determine what size of each would pass through various constricting orifices under moderate finger pressure without undergoing observable damage. The results are given in the following Table:

**TABLE**

<u>Sample Type</u>	<u>Maximum Sample Diameter in mm (inch)</u>	<u>Minimum Needle I.D. in mm (inch)</u>
PHPA Macrodisk	2.54 (0.100)	0.86 (0.034) (18ga)
PHPA Sphere	1.90 (0.075)	1.37 (0.054) (15ga)

The above results indicate that macrodisks and spheres according to the present invention compress and deform during injection to effectively reduce their outside diameter to pass through an injection needle of lesser inside diameter than the outside diameter of the macrodisk or sphere. The outside diameter of the macrodisks may be as much as about three times the inside diameter of the needle, while the diameter of the spheres may be up to about one and a half times the inside diameter of the needle.

**Claims**

1. An injectable composition consisting of a plurality of discrete physiologically-compatible, non-biodegradable, polymeric bodies, characterized in that said bodies having (i) an average outside diameter of from about 0.027 to 5.08 mm. (0.005 to 0.20 inch), (ii) reversible deformability of about 20 to 75% to their unstressed outside diameter, and (iii) a lubricious surface.
2. A composition according to claim 1, characterized in that said bodies are made from a water-swelling hydrogel.
3. A composition according to claim 2, characterized in that said hydrogel is a partially hydrolyzed polyacrylonitrile.
4. A composition according to claim 2 or 3, characterized in that said bodies also include a water-soluble polysaccharide.
5. A composition according to claim 4, characterized in that said bodies are made from a mixture of a partially hydrolyzed polyacrylonitrile and dextran.
6. A composition according to any one of the preceding claims, characterized in that said bodies are deform-

able macrodisks having an average outside diameter of from about 0.254 to 2.159 mm. (0.01 to 0.085 inch).

- 5 7. A composition according to any one of claims 1 to 5, characterized in that said bodies are spherical bodies having an average outside diameter of from about 0.254 to 2.159 mm. (0.01 to 0.085 inch).
8. A process for the preparation of an injectable composition according to claim 1, characterized in that it comprises dissolving a physiologically-compatible, non-biodegradable, water-insoluble, non-crosslinked polymer in a dipolar aprotic organic solvent, rapidly injecting the resulting solution in a fine stream into  
10 relatively large volume of a liquid medium which is a non-solvent for the polymer while slowly stirring said medium so that discrete bodies of the polymer are formed, washing said bodies until said solvent is removed and recovering bodies of the desired size by filtration through an appropriate sieve.
9. A process according to claim 8, characterized in that said polymer is a water-swellaable hydrogel.
- 15 10. A process according to claim 9, characterized in that said hydrogel is a partially hydrolyzed polyacrylonitrile.
11. A process according to any one of claims 8 to 10, characterized in that the polymer solution also includes a water-soluble polysaccharide.  
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12. A process according to claim 11, characterized in that said water-soluble polysaccharide is dextran.
13. A process according to any one of claim 8 to 12, characterized in that said dipolar aprotic organic solvent is dimethyl sulfoxide.
- 25 14. A process according to any one of claims 8 to 13, characterized in that said liquid medium is water, acetone or a low molecular weight alcohol.

### 30 Patentansprüche

1. Injizierbare Zusammensetzung, bestehend aus einer Vielzahl diskreter, physiologisch verträglicher, nicht biologisch abbaubarer Polymerkörper, dadurch gekennzeichnet, daß die Körper (i) einen durchschnittlichen Außendurchmesser von etwa 0,027 bis 5,08 mm (0,005 bis 0,20 inch), (ii) eine reversible Verformbarkeit von etwa 20 bis 75 % ihres entspannten Außendurchmessers und (iii) eine gleitfähige Oberfläche aufweisen.  
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2. Zusammensetzung nach Anspruch 1, dadurch gekennzeichnet, daß die Körper aus einem wasserquellbaren Hydrogel hergestellt sind.
- 40 3. Zusammensetzung nach Anspruch 2, dadurch gekennzeichnet, daß das Hydrogel aus einem teilweise hydrolysierten Polyacrylnitril besteht.
4. Zusammensetzung nach Anspruch 2 oder 3, dadurch gekennzeichnet, daß die Körper ferner ein wasserlösliches Polysaccharid umfassen.  
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5. Zusammensetzung nach Anspruch 4, dadurch gekennzeichnet, daß die Körper aus einem Gemisch eines teilweise hydrolysierten Polyacrylnitrils und Dextran bestehen.
- 50 6. Zusammensetzung nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß die Körper aus verformbaren Makroscheiben eines durchschnittlichen Außendurchmessers von etwa 0,254 bis 2,159 mm (0,01 bis 0,085 inch) bestehen.
7. Zusammensetzung nach einem der Ansprüche 1 bis 5, dadurch gekennzeichnet, daß die Körper aus kugelförmigen Körpern eines durchschnittlichen Außendurchmessers von etwa 0,254 bis 2,159 mm (0,01 bis 0,085 inch) bestehen.  
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8. Verfahren zur Herstellung einer injizierbaren Zusammensetzung nach Anspruch 1, dadurch gekennzeichnet, daß es ein Auflösen eines physiologisch verträglichen, nicht biologisch abbaubaren, wasserunlöslichen, nichtvernetzten Polymeren in einem dipolaren, aprotischen, organischen Lösungsmittel, ein ra-

5 sches Injizieren der erhaltenen Lösung in einem feinen Strom in ein relativ großes Volumen eines für das Polymere ein Nichtlösungsmittel darstellenden flüssigen Mediums unter langsamem Rühren des Mediums, so daß diskrete Körper des Polymeren gebildet werden, Waschen der Körper bis zur Entfernung des Lösungsmittels und Wiedergewinnen der Körper der gewünschten Größe durch Filtration durch ein geeignetes Sieb umfaßt.

9. Verfahren nach Anspruch 8, dadurch gekennzeichnet, daß das Polymer aus einem wasserquellbaren Hydrogel besteht.

10. Verfahren nach Anspruch 9, dadurch gekennzeichnet, daß das Hydrogel aus einem teilweise hydrolysierten Polyacrylnitril besteht.

11. Verfahren nach einem der Ansprüche 8 bis 10, dadurch gekennzeichnet, daß die Polymerlösung ferner ein wasserlösliches Polysaccharid umfaßt.

12. Verfahren nach Anspruch 11, dadurch gekennzeichnet, daß das wasserlösliche Polysaccharid aus Dextran besteht.

13. Verfahren nach einem der Ansprüche 8 bis 12, dadurch gekennzeichnet, daß das dipolare, aprotische, organische Lösungsmittel aus Dimethylsulfoxid besteht.

14. Verfahren nach einem der Ansprüche 8 bis 13, dadurch gekennzeichnet, daß das flüssige Medium aus Wasser, Aceton oder einem niedrigmolekularen Alkohol besteht.

## Revendications

1. Composition injectable consistant en un ensemble de corps polymériques distincts physiologiquement compatibles, non biodégradables, caractérisée en ce que lesdits corps possèdent (i) un diamètre extérieur moyen d'environ 0,027 à 5,08 mm (0,005 à 0,20 inch), (ii) une aptitude à la déformation réversible d'environ 20 à 75 % de leur diamètre extérieur non soumis à des tensions, et (iii) une surface douée d'onctuosité.

2. Composition suivant la revendication 1, caractérisée en ce que les corps sont préparés à partir d'un hydrogel pouvant gonfler dans l'eau.

3. Composition suivant la revendication 2, caractérisée en ce que l'hydrogel est un polyacrylonitrile partiellement hydrolysé.

4. Composition suivant la revendication 2 ou 3, caractérisée en ce que les corps comprennent également un polysaccharide hydrosoluble.

5. Composition suivant la revendication 4, caractérisée en ce que les corps sont préparés à partir d'un mélange d'un polyacrylonitrile partiellement hydrolysé et de dextrane.

6. Composition suivant l'une quelconque des revendications précédentes, caractérisée en ce que les corps sont des macrodisques déformables ayant un diamètre extérieur moyen d'environ 0,254 à 2,159 mm (0,01 à 0,085 inch).

7. Composition suivant l'une quelconque des revendications 1 à 5, caractérisée en ce que les corps sont des corps sphériques ayant un diamètre extérieur moyen d'environ 0,254 à 2,159 mm (0,01 à 0,085 inch).

8. Procédé de préparation d'une composition injectable suivant la revendication 1, caractérisé en ce qu'il comprend la dissolution d'un polymère non réticulé insoluble dans l'eau, non biodégradable, physiologiquement compatible dans un solvant organique aprotique dipolaire, l'injection rapide de la solution résultante en un courant fin dans un volume relativement grand d'un milieu liquide qui est un non-solvant pour le polymère avec agitation lente simultanée dudit milieu de telle sorte que des corps distincts du polymère soient formés, le lavage desdits corps jusqu'à élimination dudit solvant, et la séparation des corps ayant les dimensions désirées par filtration à travers un tamis approprié.

9. Procédé suivant la revendication 8, caractérisé en ce que le polymère est un hydrogel pouvant gonfler dans l'eau.
- 5 10. Procédé suivant la revendication 9, caractérisé en ce que l'hydrogel est un polyacrylonitrile partiellement hydrolysé.
11. Procédé suivant l'une quelconque des revendications 8 à 10, caractérisé en ce que la solution de polymère comprend également un polysaccharide hydrosoluble.
- 10 12. Procédé suivant la revendication 11, caractérisé en ce que le polysaccharide hydrosoluble est le dextrane.
13. Procédé suivant l'une quelconque des revendications 8 à 12, caractérisé en ce que le solvant organique aprotique dipolaire est le diméthylsulfoxyde.
- 15 14. Procédé suivant l'une quelconque des revendications 8 à 13, caractérisé en ce que le milieu liquide est l'eau, l'acétone ou un alcool de bas poids moléculaire.

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